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Original article

Psychiatric comorbidities in patients with systemic lupus erythematosus: a systematic review of the last 10 years

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ABSTRACT

Objective: To analyze the frequency of psychiatric comorbidities in patients with systemic lupus erythematosus (SLE) using the systematic review method.
Methods: A systematic literature search was performed between April and July 2011 in the following databases: BIREME, PubMed and CAPES thesis database. This search prioritized studies published over the last ten years (2001-2011), involving the presence of psychiatric comorbidities in patients with SLE.
Results: Out of 314 articles published in scientific journals (PubMed) and 29 (BIREME), previously identified ones, 13 articles on psychiatric disorders and SLE were selected so they could be submitted to the systematic review methodological approach. The articles indicated high frequency of psychiatric comorbidities, especially mood and anxiety disorders. There is no consensus between the disease activity and psychiatric disorders. Patients with active SLE showed a higher risk of developing mood disorders than patients with inactive SLE.
Conclusion: Patients with SLE had a higher suicide risk than the general population. More thorough studies to evaluate the psychological and genetic role, specific and non-specific autoimmune inflammatory mechanisms in mood and anxiety disorders are needed.

Comorbidades psiquiátricas em pacientes com lúpus eritematoso sistêmico: uma revisão sistemática dos últimos 10 anos

Palavras-chave:
Lúpus eritematoso sistêmico
Psiquiatria
Transtornos mentais

RESUMO

Objetivo: Verificar a frequência de comorbidades psiquiátricas em pacientes com lúpus eritematoso sistêmico (LES), a partir do método da revisão sistemática.
Métodos: Uma busca sistemática na literatura foi realizada no período entre abril e julho de 2011, nos portais: BIREME, PubMed e banco de teses da CAPES. Essa busca priorizou estudos publicados nos últimos 10 anos (2001-2011), que envolvessem a presença de comorbidades psiquiátricas em pacientes com LES.
Resultados: De 314 artigos publicados em periódicos científicos (PubMed) e 29 artigos (BI-

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REME) previamente identificados e selecionados, foram selecionados 13 artigos sobre transtornos psiquiátricos e LES para submissão à abordagem metodológica de uma revisão sistemática. Os artigos indicaram alta frequência de comorbidades psiquiátricas, principalmente transtornos do humor e de ansiedade. Não há um consenso entre a atividade da doença e os transtornos psiquiátricos. Pacientes com atividade da doença apresentaram um risco maior de desenvolver transtorno do humor do que pacientes com doença inativa. Pacientes com LES apresentaram mais risco de suicídio do que a população em geral.
Conclusão: Estudos mais detalhados para avaliar o papel psicológico, genético, mecanismos autoimunes específicos e não específicos inflamatórios nos transtornos do humor e de ansiedade são necessários.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory and autoimmune disease of multifactorial etiology that can affect many organs and systems.[1] The studies show a higher prevalence in women (approximately 90% of cases), especially during childbearing years, i.e. between 15 and 45 years of age; more common in women of black ethnicity than in Caucasian ones at a ratio of 3:1 , but it can occur in all ethnic groups and geographic regions.[2]

The central nervous system is often affected by this disease, causing neurological and/or psychiatric symptoms.[1-3] The prevalence of neuropsychiatric disorders in SLE reported in the literature is variable (14-75%), reflecting the variation in diagnostic criteria and selection of the study population, which can manifest at any time during the course of the disease with different clinical forms, from mild to severe ones.[4] Psychological stress is considered by many academics as being of particular importance in triggering the disease and its exacerbations.[5-7] Psychiatric syndromes in patients with SLE include a variety of psychiatric findings causing chronic disabilities.[8]

The American College of Rheumatology (ACR) classified 19 neuropsychiatric syndromes related to SLE, describing them as psychiatric manifestations, psychosis, mood disorders, anxiety disorders and acute confusional state.[1]

Thus, during the clinical treatment of patients, in addition to the need to consider the disease itself, it would be appropriate to observe the specific psychiatric manifestations and determine how these comorbidities result in daily life activity limitations, affecting the quality of life of the individual.[9]

The aim of this review is to assess the frequency of psychiatric comorbidities in patients with SLE.

Material and methods

A systematic literature search was performed between April and July of 2011 at the following databases: BIREME, PubMed and CAPES thesis database. This search prioritized studies published in the last 10 years (2001-2011) that included the presence of psychiatric comorbidities in patients with SLE.

The aim of this study was to collect and synthesize research results systematically. For this purpose, our guiding question was: What is the frequency of psychiatric comorbidities in patients with SLE? Thus, the expected primary outcome is that psychiatric comorbidities are frequent and identified at some level of SLE activity. As secondary outcome, it is likely that among the observed comorbidities, depression is the most frequent among SLE patients.

Aiming to clearly define the pertinence of the literature found for this review study, the following inclusion criteria were established: a) articles with human subjects; b) articles published in the last 10 years; c) patients of both genders; d) aged 19 years and older; e) articles published in English, Portuguese and Spanish; and f) prospective studies.

The exclusion criteria were developed to eliminate articles that did not follow these parameters in their methodology: a) review studies; b) short communications; c) qualitative studies; d) publications in other languages, even when they had an abstract in English; e) intervention studies; f) and case reports.

The search was performed by three researchers. Two researchers (NMJA and MGWS) were responsible initially for independent and blind searches. A third investigator (OGL), the reviewer, was consulted in cases of disagreement to establish a consensus. The data collection forms were standardized and created before the search was started.

The key words were chosen according to the DeCS/MeSH list. The DeCS list had the following key words: Systemic Lupus Erythematosus and Psychiatry. The MeSH list had the following ones: Lupus Erythematosus, Systemic and Psychiatry (Table 1). The references from selected articles were also reviewed to identify other relevant studies that might have been omitted during the electronic search.

The search was carried out in more than one site and several databases including thesis and dissertation databases. The search strategy followed the recommendations by Castro et al.,[10] Dickersin et al.[11] and the Cochrane Collaboration.

All articles obtained in the search were organized in tables and evaluated regarding the condition of being included or excluded based on the eligibility criteria. The Jadad Scale[12] was applied to evaluate the included articles, in which each positive response generates 1 point on the scale, resulting in a score of 0-5 points:

1 a. Was the study described as randomized?
1 b. Was the method adequate?

2 a. Was the study described as double-blind?
2 b. Was the method adequate?
3. Was there a description of losses and exclusions?

Results

After the first search, using the expression from item 3 (Table 1) and without using the inclusion criteria, a total of 1,504 articles were identified in the PubMed site and 5,179 articles in the BIREME site.

Of the 1,504 items in the PubMed site, 266 articles were immediately eliminated as they were review articles, of which 1,238 remained to be assessed. After a more careful analysis following the inclusion criteria, of the 1,238 articles, 314 were selected.

Of the 314 articles analyzed at PubMed, 290 were excluded for the following reasons: a) case reports (18); b) neuroimaging study (33); c) autoantibody research (26); d) qualitative study (32); e) experimental study (13); f) evaluation of drug treatment (32); g) study with children and adolescents (7); h) analysis of cognitive deficits (32); i) studies with other autoimmune diseases (97). A total of 11 articles remained in the systematic review.

In the BIREME database, of the 5.179 articles that were identified, 29 were selected, of which four were identical to those found in PubMed database; thus, of the 25 remaining articles, only one was included in this review, for meeting the inclusion criteria.

Two theses were found in the CAPES thesis database, but only one was selected; however, it was not possible to obtain its full text. The other thesis was excluded after reading its title.

The references of the 11 articles (PubMed) and one article (BIREME) included were analyzed and only one article met the inclusion criteria, and thus it was selected.
Therefore, the study of this systematic analysis included 13 articles (Fig. 1).

In this systematic review, 11 articles achieved the highest score 5 on the Jadad scale.[12] The number of subjects varied from 46-1,206. The age studied had a wide range (16-83 years). Mean age ranged from 32-48 years. The vast majority of subjects in the different studies (87-100%) were females (Table 2). Only three studies evaluated the age of diagnosis, which was around 30 years. Disease duration ranged from a few months in the study by Hanly et al.[24] to 47 years in the study by Bachen et al.[22] The mean duration of the disease ranged around nine years.

Most articles used the SLEDAI[25] tool to evaluate disease activity, whereas many tools were indicated for psychiatric evaluation, considering the terms of the DSM-IV.[26]

The most frequent psychiatric comorbidities were mood disorders and anxiety disorders. Major depressive episode (MDE) was the most frequent mood disorder, ranging from 18.3-75%, whereas anxiety disorder not otherwise specified (AD-NOS) was the most frequent among the anxiety disorders, ranging from 3.6-74.6%.

Subsequently, the most commonly found anxiety Disorders were: generalized anxiety disorder (GAD) 9.9%,[21] 4.3%[22] and 2.4%,[8] obsessive-compulsive disorder (OCD) 8.9%,[22] 42%[19] and 3.6%,[8] social phobias and specific phobia (SCP and SP) 12.7% and 25.4%,[21] 15.6% and 23.9% [22] and 1.2% and 1.2%.[8]

Among other psychiatric comorbidities found, suicide risk (SR) was observed by Ishikura et al. (8.3%)[14] and Jarpa et al. (9.6%),[8] psychotic syndrome (SP) by Hanly et al. (5.0%)[24] and Jarpa et al. (1.2%),[8] adaptation disorder (AD) by Nery et al. (8.4%)[21] and Jarpa et al. (2.4%)[8]. Table 3 summarizes the frequency of psychiatric comorbidades and evaluates articles according to Jadad criteria.[12]

Table 1 – Expressions used in the search (Mesh).

Expressions	N. of articles (Database)
1: lupus erythematosus, systemic	49,637 (PubMed)
2: psychiatry OR psychiatric OR mental disorders OR depression OR emotional disorders OR anxiety disorders OR mood disorders	1,148,148 (PubMed)
3: #1 AND #2	1,504 (PubMed)
Limits: human, English, Portuguese or Spanish, male, female, age older than 19 years, published over the past 10 years	314 (PubMed)
Maintained after exclusion criteria	11 (PubMed)
Added after reference consultation	1 (PubMed)
Added after consultation	1 (BIREME)
Included in this review	13

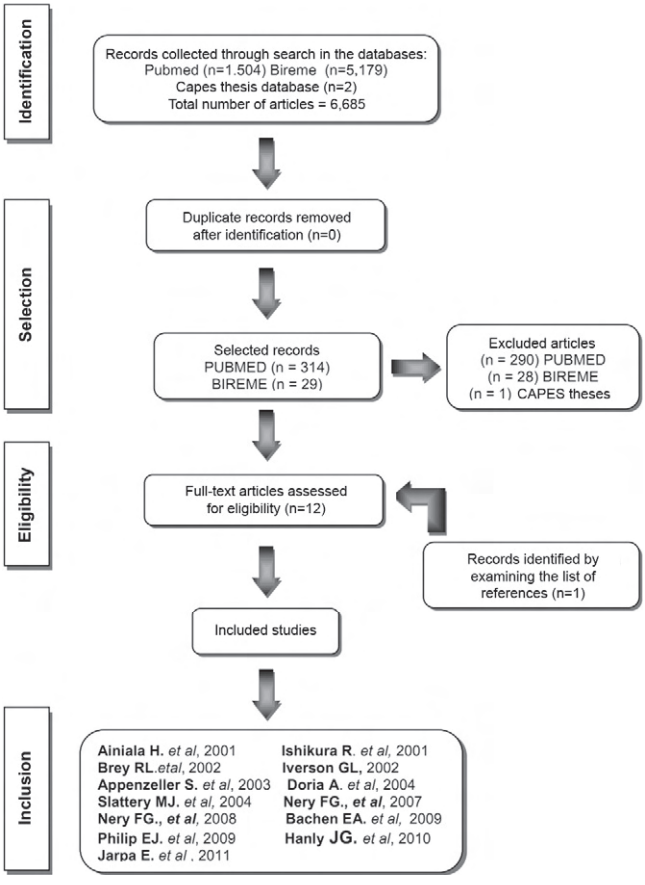

Fig. 1 – Study search and selection for the systematic review according to Cochrane Collaboration

Table 2 – Clinical and demographic characteristics of the 13 articles of the systematic review in patients with SLE in the past 10 years.

Author	n	Age (years)	Gender	Age at diagnosis (years)	Duration (years)	DAI
Ainiala	46	45 ± 13 (20-64)	39♀, 7♂	-	14 ± 8 (2-37)	ECLAN
Ishikura	84	41 ± 12 (20-68)	84♀	31 ± 10 (14-60)	11 ± 7 (1-29)	LACC
Brey	128	43 (21-71)	120♀, 8♂	-	8 (0.2-37)	SLEDAI SLICC
Iverson	103	48 ± 13	102♀, 1♂	-	-	-
Appenzeller	40	32	37♀, 3♂	-	-	SLEDAI
Doria	126	39 ± 12 (18-65)	110♀, 16♂	-	10 ± 6 (1-32)	ECLAN SLICC
Slattery	50	42.1 ± 11.1 (20-71)	45♀, 5♂	26.8 ± 10.3(7-60)	15.3 ± 9.1(1-34)	-
Nery	71	35 ± 10 (19-65)	71♀	-	10 ± 7 (0-29)	SLEDAI SLICC
Nery	71	35 ± 10 (19-65)	71♀	-	10 ± 7 (0-29)	SLEDAI SLICC
Bachen	326	48 ± 11 (18-83)	326♀	33 ± 12 (1-73)	15 ± 10 (1-47)	SLAC
Philip	154	52 ± 15	140♀, 14♂	-	15 ± 10	-
Hanly	1206	35 ± 13	1080♀, 126♂	-	5(4) months	SLEDAI SLICC
Jarpa	83	39 (16-72)	76♀, 7♂	-	5 (0.1-40)	SLEDAI-2K

DAI, disease activity index; ECLAN, European Consensus Lupus Activity Measure; LACC, Lupus Activity Criteria Count; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLAC, Systemic Lupus Activity Questionnaire.

Discussion

Psychiatric symptoms are commonly reported in patients with SLE, contributing to the physical and functional morbidity. That was verified in the articles analyzed in this systematic review.[8,13-24]

Although the study design did not represent an exclusion criterion, only Jarpa et al.[8] and Hanly et al.[24] described their studies as being prospective. However, considering the description of the procedures in the other studies, one could say that the design would also be prospective, cross-sectional or longitudinal.

The eligibility criteria were described in detail in all articles, providing subsidies for future studies. By applying more stringent inclusion criteria, thus substantially reducing the number of articles, allowed greater consistency, homogeneity and reliability of the analyzed findings.

The size of the samples studied in the thirteen articles was widely variable, depending mainly on the study aim and methodology used. While Ainiala et al.[13] described the prevalence of neuropsychiatric syndromes in a Finnish population represented by 46 subjects, Hanly et al.[24] carried out a multicenter study to determine the frequency, the monitoring of neuropsychiatric events and their impact on quality of life in the first three years of the disease, obtaining a much larger sample of 1,206 subjects.

The mean disease duration was similar between articles, lasting approximately 10 years. The samples of subjects with SLE were predominantly female in all articles (87-100%). Male subjects were analyzed in 9 articles, but no characteristics of this group were recorded separately among the results.[8,13,15-19,23,24] Some articles had in common an evaluation regarding the contribution of social factors, mainly those related to ethnicity in subjects with SLE.[8,15,24,14,18]

Jarpa et al.[8] described for the first time the prevalence of psychiatric disorders in Chilean patients of mixed blood (Amerindian/Spanish) with a diagnosis of SLE, observing considerably higher frequencies than those seen in the general population and no association with disease activity. Brey et al.[15] studied a predominantly Mexican-American population, comprising much of the San Antonio (Texas) region, where psychiatric disorders in patients with SLE were also very frequent.

Ainiala et al.,[13] when analyzing 46 Finnish subjects with a diagnosis of SLE, found that 42 patients met at least one neuropsychiatric criterion established by the ACR.

The studies by Iverson[16] and Hanly et al.[24] observed a predominance of Caucasians among the several ethnic groups studied. Bachen et al.[22] described the prevalence of mood and anxiety disorders in Caucasian women and Slattery et al.,[19] analyzing the prevalence of OCD in SLE patients, found that 71% of patients were Caucasians.

The most widely used tool in the assessment of disease activity was SLEDAI,[25] which has been used for the assessment of disease activity in multiple centers with good results regarding its validity and reproducibility. In some studies this tool did not contribute to the association between the presence of psychiatric disorders and disease activity, perhaps by the diversity of disorders present in this sample, including different forms of anxiety and alcoholism or probably because mechanisms that are intrinsic to SLE may participate in the pathogenesis of each psychiatric disorder.[8,21] On the other hand, the study by Nery et al. [20] reported a trend of association between MDE with disease activity.

In this review, the studies by Iverson,[16] Slattery et al.[19] and Philip et al.[23] have not applied any tool to assess disease activity, as their objectives did not include the analysis of this activity.

Articles trying to define the prevalence of psychiatric disorders showed variations regarding patient selection, type of study and clinical definitions of psychiatric comorbidities, contributing to different results.[8, 13-24]

During the course of the disease, depression and anxiety symptoms have been often observed by several authors.[8,17,18,21,22] In this systematic review, the most common psychiatric comorbidity was MDE, ranging from 18.3-75% in different studies.[8,13,15-18,20,22,23] The negative perception of the disease would be associated with different levels of depres-

Table 3 – Frequency of psychiatric comorbidity in patients with SLE from 13 articles of the systematic review of the past 10 years.

Author	Year	PAT	Mood disorders		Anxiety disorders		Others		Jadad
Ainiala	2001	BDI	39.6%	MDE	13%	AD-NOS			5
			4.4%	BD-NOS					
Ishikura	2001	SDS	40.5%	DD-NOS	51.2%	AD-NOS	8.3%	SR	5
		STAI							
		CMI							
Brey	2002	SCID	28%	MDE	24%	AD-NOS	5%	PD-NOS	5
			19%	DD-NOS					
			4%	BD-NOS					
Iverson	2002	BCMDI	39%	MDE					4
		BDI							
Appenzeller	2003	BPRS	75%	MDE	70%	AD-NOS			3
		HAD							
		BECK							
Doria	2004	HAS	40.5%	MDE	74.6%	AD-NOS			5
		HAM-D							
Slattery	2004	Y-BOCS			42%	OCD			5
Nery	2007	SCID	22.5%	MDE					5
			4.2%	DD-NOS					
Nery	2008	SCID	22.5%	MD	1.4%	AG	1.4%	SD	5
			18.3%	MDE	12.7%	SCP	1.4%	AA	
			4.2%	THCMG	25.4%	SP	8.4%	AD	
			4.2%	DD-NOS	9.9%	GAD			
					12.7%	AD-NOS			
Bachen	2009	CIDI	47%	MDE	1.2%	AG			5
			6%	BD I	4.3%	GAD			
			3.3%	DD	8.9%	OCD			
					15.6%	SCP			
					23.9%	SP			
					15.6%	PD			
Philip	2009	CDS	27%	MDE					5
Hanly	2010	ACR	18.2%	MD-NOS			5.0%	SP	5
Jarpa	2011	MINI- plus	21.7%	MDE	3.6%	AD-NOS	11.7%	PDD	5
			4.8%	DD	3.6%	AG	3.6%	MADD	
			2.4%	ME	3.6%	OCD	1.2%	SP	
					2.4%	GAD	9.6%	SR	
					2.4%	PTSD	6.0%	BDD	
					1.2%	SCP	2.4%	AD	
					1.2%	SP			

PAI, Psychiatric Assessment Tool; AA, Alcohol Abuse; AG, Agorafobia; BCMDI, British Columbia Major Depression Inventory; BDI, Beck Depression Inventory; CDS, Cardiac Depression Scale; CIDI, Composite International Diagnostic Interview; CMI, Cornell Medical Index; MD, Major Depression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; MDE, Major Depressive Episode; ME, Maniac Episode; SP, Specific Phobia; SCP, Social Phobia; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; MADD, Mixed anxiety-depressive disorder; MINI-plus, Mini International Neuropsychiatric Interview; SR, Suicide Risk; SCID, Structured Clinical Interview for Psychiatric Diagnosis; SDS, Self-rating Depression Scale; PS, Psychotic Syndrome; STAI, State-Trait Anxiety Inventory; AD, Adaptation Disorder; GAD, Generalized Anxiety Disorder; AD-NOS, Anxiety Disorder-Not Otherwise Specified; BD I, Bipolar Disorder I; BD-NOS, Bipolar Disorder-Not Otherwise Specified; DD, Dysthymic Disorder; BDD, Bodily Dysmorphic Disorder; PDD, Premenstrual Dysphoric Disorder; DD-NOS, Depressive Disorder Not Otherwise Specified; PTSD, Posttraumatic stress disorder; MD-NOS, Mood disorder not otherwise specified; OCD, Obsessive-Compulsive Disorder; PD,Panic Disorder; PD-NOS, Psychotic Disorder Not Otherwise Specified; SD, Somatoform Disorder.

sion in these patients. [23] Several articles have also found a significant prevalence of depressive disorder not otherwise specified in these patients.[14,15,20,21]

Anxiety disorders have also been described as having a high prevalence in SLE among the several articles,[8,13-15,17-19,21,22] especially AD-NOS, Phobias, OCD and GAD. According to these authors, the reason why the high prevalence of anxiety disorders is considered unknown, is justified by the fact that anxiety has not been well studied in patients with SLE. Patients with anxiety disorder often find it difficult to reveal their symptoms, thus necessitating other evaluation methods such as self-reporting questionnaires for the identification of this comorbidity.[22]

The OCD is a common comorbidity in patients with SLE, according to the articles by Jarpa et al.,[8] Bachen et al.[22] and mainly Slattery et al.[19] The purpose of this latter study would be to identify, among psychiatric symptoms in subjects with SLE, which specific prevalence of this disorder could be higher than in community-based studies. Neuroimaging studies indicate changes in the basal ganglia in patients with OCD.[27,28] Evidence suggests an association between these abnormalities and psychiatric symptoms in this population.[29]

Other psychiatric comorbidities were reported as: SR, psychotic disorder, AD, body dysmorphic disorder.[8,14,15,21,24] SR is not evaluated by the criteria of the ACR[30] and appears to be neglected in this study population. Jarpa et al.[8] found a high prevalence (9.6%) compared with the general population. Suicidal ideation was observed in 8.3% in the study by Ishikura et al.[14] and was correlated with troubled relationships with family members, emphasizing the importance of family support for these patients.

Articles in this systematic review indicated a high frequency of psychiatric comorbidities in subjects with SLE, especially mood and anxiety disorders.

There is no consensus yet for the correlation between disease activity and several mental disorders, although the articles showed some methodological differences, mainly related to the description of the study design, the characterization of the sample and the different evaluation tools and questionnaires. Patients with disease activity had a higher risk of developing mood disorders than patients with inactive disease, regardless of the occurrence of stressful events or susceptibility to recurrent major depressive disorder.

The recognition of these associations can provide a more appropriate treatment of these patients and may also bring new knowledge to the understanding of the mechanisms involved in this important clinical presentation of SLE.

In this review study previous observations of the high frequency of depressive and anxiety disorders in SLE without concomitant neurological manifestations were evident.

The association between SLE and depression deserves special attention, especially concerning suicide risk, as it can be observed that SLE patients have a higher risk of suicide than that of the general population. In this review, the most often observed anxiety disorder was the anxiety disorder not otherwise specified.

More detailed studies to assess the psychological and genetic role, specific and non-specific inflammatory autoimmune mechanisms in mood and anxiety disorders are needed.

Despite the technological and scientific advances, SLE remains a threatening disease with a chronic evolution, resulting in intense physical, psychological and social suffering. Further studies are necessary, with a larger number of subjects with SLE, using standardized scales and tools.

Even non-psychiatrists should be able to recognize symptoms suggestive of mental disorders, especially in SLE outpatient clinics and refer these patients to specialized treatment, in order to reduce suffering caused by this disease.

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